UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/534,424	05/10/2005	Kaoru Miyamoto	1680/7	4728

25297 7590 08/26/2010

JENKINS, WILSON, TAYLOR & HUNT, P. A.
Suite 1200 UNIVERSITY TOWER
3100 TOWER BLVD.,
DURHAM, NC 27707

EXAMINER	
DUNSTON, JENNIFER ANN	
ART UNIT	PAPER NUMBER
1636	

MAIL DATE	DELIVERY MODE
08/26/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/534,424	MIYAMOTO ET AL.	
	Examiner	Art Unit	
	Jennifer Dunston	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,7,8 and 12-14* is/are pending in the application.

4a) Of the above claim(s) *7,8 and 12* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,13 and 14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 May 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/16/2010*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 6/16/2010, in which claims 1 and 13 were amended, and claim 14 was newly added. Claims 1, 7, 8 and 12-14 are pending.

Applicant's arguments have been thoroughly reviewed, but are not persuasive for the reasons that follow. Any rejections and objections not reiterated in this action have been withdrawn. **This action is FINAL.**

Election/Restrictions

Applicant's election without traverse of Group I in the reply filed on 8/2/2007 is acknowledged.

Claims 7, 8 and 12 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 8/2/2007.

Claims 1, 13 and 14 are under consideration.

Information Disclosure Statement

Receipt of an information disclosure statement, filed on 6/16/2010, is acknowledged. The signed and initialed PTO 1449 has been mailed with this action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 13 and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection**.

In the amendment filed 6/16/2010, claims 1 and 13 were amended to require a drug agent comprising a dimer of ZHX3 and ZHX1 as an effective component.

In light of the teachings of the specification, the term "drug agent" is interpreted as a composition formulated for be administered for the treatment of disease, specifically hepatoma (e.g., page 3, lines 20-32). The specification envisions "drug agents" comprising a ZHX3 protein or peptide (e.g., page 3, lines 26-32). In the case of "drug agents", the ZHX3 protein is separated from its natural source so that it can be administered as a therapeutic product. However, the specification does not describe a drug agent comprising a dimer of ZHX3 and ZHX1, as now required by the claims. Dimers of ZHX3 and ZHX1 are disclosed in the originally filed specification as present in a two-hybrid assay system or GST pull-down assay (e.g., page 4, line 18 to page 5, line 9; Figures 3-5). The specification discloses yeast cells and HEK293 cells containing plasmids expressing ZHX1 and ZHX3 fusion proteins, where the heterodimers are found within the cells (e.g., page 12, Reference example 5; pages 13-14, Reference example 7; pages 16-18, Example 2; pages 19-20, Example 5). The specification also discloses GST-ZHX1 and GST-ZHX3 fusion proteins labeled with ^{35}S for *in vitro* pull down assays (e.g., page 13, Reference example 6). Furthermore, the ZHX3 of the dimers disclosed in the working examples

does not consist of the sequence of SEQ ID NO: 1. Other sequence is present and/or absent relative to SEQ ID NO: 1.

The reply filed 6/16/2010 asserts that support for the amendment can be found throughout the specification as originally filed, and in particular at page 2, lines 23-32; page 17, lines 15-19; page 17, line 31 through page 18, line 23, and page 22, line 26 through page 23, line 8.

Page 2, lines 23-32 summarizes the results of the experiments disclosed in the specification. Specifically, it was discovered that ZHX1 interacts with ZHX3 in the nuclei of cells, where the dimer functions to repress transcription. Pages 17, 18, 22 and 23 disclose the interaction of ZHX1 and ZHX3 in the context of a two-hybrid assay or in the context of a GST pull-down assay and do not disclose a drug agent. Thus, the portions of the specification cited by Applicant do not provide support for a drug agent comprising the dimer of ZHX1 and ZHX3.

In the amendment filed 6/16/2010, new claim 14 was added. New claim 14 requires the drug agent of claim 1 to further comprise a cofactor selected from the group consisting of mSin3A, mSin3B, histone deacetylase, N-CoR, BS69 and ATF-IP.

The specification does not disclose a drug agent comprising a ZHX3-ZHX1 heterodimer, where the composition further comprises a cofactor selected from the group consisting of mSin3A, mSin3B, histone deacetylase, N-CoR, BS69 and ATF-IP. The specification teaches that BS69 corepressor interacts with ZHX1 in the context of a yeast two-hybrid system, where the entire sequence of human ZHX1 was fused to the GAL4 DBD and a rat liver and granulosa cell cDNA library was screened (e.g., pages 14-15, Example 1). The specification teaches that ATF-IP interacts with ZHX1 in the context of a yeast two-hybrid system, where the entire

sequence of human ZHX1 was fused to the GAL4 DBD and a rat liver and granulosa cell cDNA library was screened (e.g., pages 14-15, Example 1). Under the disclosed conditions ZHX1 and BS69, or ZHX1 and ATF-IP interact within the cell in the absence of ZHX3. Furthermore, the specification suggests that ZHX1 and ZHX3 could interact with the other co-repressors (e.g., paragraph bridging pages 22-23). However, the specification does not disclose a drug agent comprising a ZHX1-ZHX3 dimer and a co-repressor.

The reply filed 6/16/2010 asserts that support for the amendment can be found throughout the specification as originally filed, and in particular page 2, lines 23-32, page 17, line 31 through page 18, line 23, and page 22, line 26 through page 23, line 8.

Page 2, lines 23-32 summarizes the results of the experiments disclosed in the specification. Specifically, it was discovered that ZHX1 interacts with ZHX3 in the nuclei of cells, where the dimer functions to repress transcription. Pages 17, 18, 22 and 23 disclose the interaction of ZHX1 and ZHX3 in the context of a two-hybrid assay or in the context of a GST pull-down assay and do not disclose a drug agent. The paragraph bridging pages 22-23 discloses that ZHX1 and ZHX3 could interact with other co-repressors; however, the specification only provides evidence that ZHX1 interacts with BS69 or ATF-IP in the absence of ZHX3. The specification does not disclose a drug agent containing a dimer of ZHX1 and ZHX3 and a cofactor selected from mSin3A, mSin3B, histone deacetlyase, N-CoR, BS69 or ATF-IP.

The original specification, drawings and claims were thoroughly reviewed and no support could be found for the amendment. Accordingly, the amendment is a departure from the specification and claims as originally filed, and the passages that Applicant has provided do not provide support.

Claims 1, 13 and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This is a new rejection, necessitated by the amendment of claims 1 and 13, and the addition of claim 14 in the reply filed 6/16/2010.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Nature of the invention: The claims are drawn to drug agents comprising a dimer of ZHX3 and ZHX1 as an effective component, where the dimer must repress transcription of type II hexokinase or pyruvate kinase M gene in hepatoma cells. Claim 1 requires ZHX3 to comprise amino acids 1-107 and 242-555 of SEQ ID NO: 1 and have at least 85% sequence identity to SEQ ID NO: 1. Claim 13 requires ZHX3 of the dimer to consist of SEQ ID NO: 1. Claim 14 further requires the drug agent of claim 1 to contain a cofactor selected from the group consisting of mSin3A, mSin3B, histone deacetylase, N-CoR, BS69 and ATF-IP. The nature of the invention is complex in that the claimed drug agent must be capable of repressing genes specific to hepatoma, including type II hexokinase and pyruvate kinase M, in a manner sufficient to have a therapeutic effect.

Breadth of the claims: The claims are specifically drawn to a "drug agent", which must be capable of providing a therapeutic effect.

Guidance of the specification and existence of working examples: The specification asserts that it is known in the prior art that pyruvate kinase M gene and type II hexokinase gene are genes for the glycolytic pathway that are specifically induced in hepatoma (e.g., page 1). The specification states that NF-Y is a common transcription factor for both genes but is not differentially expressed between normal liver and hepatoma cells (e.g., page 1). Further, the specification teaches that ZHX1 interacts with NF-Y and is ubiquitously expressed (e.g., page 1). As with ZHX1, ZHX3 is ubiquitously expressed (e.g., page 16, lines 17-22).

The present specification teaches the identification of ZHX3 (SEQ ID NO: 1), which is a protein that interacts with ZHX1 in the context of two-hybrid assays and GST pull-down assays. The specification envisions "drug agents" comprising a ZHX3 protein or peptide (e.g., page 3, lines 26-32). In the case of "drug agents", the ZHX3 protein is separated from its natural source so that it can be administered as a therapeutic product. However, the specification does not explicitly teach a drug agent comprising a dimer of ZHX3 and ZHX1, as now required by the claims. Dimers of ZHX3 and ZHX1 are disclosed in the originally filed specification as present in a two-hybrid assay system or GST pull-down assay (e.g., page 4, line 18 to page 5, line 9; Figures 3-5). The specification discloses yeast cells and HEK293 cells containing plasmids expressing ZHX1 and ZHX3 fusion proteins, where the heterodimers are found within the cells (e.g., page 12, Reference example 5; pages 13-14, Reference example 7; pages 16-18, Example 2; pages 19-20, Example 5). The specification also disclosesGST-ZHX1 and GST-ZHX3 fusion proteins labeled with ^{35}S for *in vitro* pull down assays (e.g., page 13, Reference example 6).

The specification does not teach a drug agent comprising a ZHX3-ZHX1 heterodimer, where the composition further comprises a cofactor selected from the group consisting of mSin3A, mSin3B, histone deacetylase, N-CoR, BS69 and ATF-IP. The specification teaches that BS69 corepressor interacts with ZHX1 in the context of a yeast two-hybrid system, where the entire sequence of human ZHX1 was fused to the GAL4 DBD and a rat liver and granulosa cell cDNA library was screened (e.g., pages 14-15, Example 1). The specification teaches that ATF-IP interacts with ZHX1 in the context of a yeast two-hybrid system, where the entire sequence of human ZHX1 was fused to the GAL4 DBD and a rat liver and granulosa cell cDNA library was screened (e.g., pages 14-15, Example 1). Under the disclosed conditions ZHX1 and BS69, or ZHX1 and ATF-IP interact within the cell in the absence of ZHX3. Furthermore, the specification suggests that ZHX1 and ZHX3 could interact with the other co-repressors (e.g., paragraph bridging pages 22-23). However, the specification does not disclose a drug agent comprising a ZHX1-ZHX3 dimer and a co-repressor.

No working examples are provided that demonstrate the ability to deliver a drug agent containing a ZHX1-ZHX3 dimer, with or without an additional cofactor, to treat hepatoma or to alter the expression of pyruvate kinase M gene or type II hexokinase gene in any model.

Predictability and state of the art: The declaration filed 3/17/2008 provides evidence that ZHX3 can repress the transcription of the rat PKM gene and rat HKII gene in SL2 cells lacking all members of the ZHX family of transcription factors, except for the exogenously added ZHX3. The declaration does not provide evidence that a dimer of ZHX1-ZHX3 can be delivered to a cell, with or without additional cofactors, as a drug agent to repress type II hexokinase or pyruvate M kinase expression.

For the claimed dimers to regulate gene expression, the dimers must be delivered inside the cell. Zelphati et al (The Journal of Biological Chemistry, Vol. 276, No. 37, pages 35103-35110, September 2001) teach that few methods existed for the intracellular delivery of proteins at the time the invention was made (e.g., paragraph bridging pages35108-35109). Those methods include the addition of a protein transduction domain (PTD) to the protein interest, transfection, microinjection, and the use of cationic lipid formulations (e.g., page 35103, paragraph bridging columns). These techniques have had varying degrees of success (e.g., page 35103, paragraph bridging columns). Of these techniques the use of PTD and lipid formulations could potentially have *in vivo* applications. However, Zelphati et al teach that the efficiency of delivery by PTD varies depending on the protein delivered (e.g., page 35103, paragraph bridging columns). Further, the addition of a PTD to a protein of interest can have unpredictable effects on the biological activity of the protein (e.g., page 35109, left column, 1st full paragraph). Furthermore, successful intracellular delivery of proteins to cultured cells required serum-free conditions for the first four hours of incubation (e.g., page 35105, left column, last full paragraph). Zelphati et al teach that the structure of the protein and concentration of the protein delivered has an effect on the number of cells that take up the protein and the quantity of protein found within each of the cells (e.g., page 35105, paragraph bridging columns; page 35109, paragraph bridging columns). Further, the lipid formulation alone can be toxic to cells (e.g., page35107, paragraph bridging columns). While the lipid formulations may be somewhat effective in the cell culture setting, they pose significant problems for *in vivo* applications, including the inability to function in the presence of serum and the relatively large size of the complex, which increases clearance from the circulation and reduces the bioavailability (Ye et al.

Pharmaceutical Research, Vol. 19, No. 9, pages 1302-1309, September 2002; e.g., Abstract, paragraph bridging pages 1308-1309). Accordingly, at the time the invention was made it would have been unpredictable to deliver a therapeutically effective amount of the drug agents containing the dimer and drug agents containing the dimer and cofactor to the appropriate cells using the techniques available in the art.

Amount of experimentation necessary: The quantity of experimentation is large, as one could not rely on the teachings of the instant specification or prior art to make a drug agent comprising the claimed protein dimers, with or without a cofactor protein, where the drug agent is capable of being used to repress the transcription of type II hexokinase or pyruvate kinase M and treat hepatoma. It would require a large amount of inventive effort to develop a process of intracellular protein delivery that is not limited by the size of the dimeric transcription factor, with or without a cofactor protein, or the presence of serum and that does not alter the ability of the protein to regulate gene expression.

In view of the breadth of the claims and the lack of guidance provided by the specification as well as the unpredictability of the art, the skilled artisan would have required an undue amount of experimentation to make and/or use the claimed invention. Therefore, claims 1, 13 and 14 are not considered to be enabled by the instant specification.

Response to Arguments - 35 USC § 102

The rejection of claims 1 and 13 under 35 U.S.C. 102(b) as being anticipated by UniProt Accession No. Q9H4I2 has been withdrawn in view of Applicant's amendment to the claims in the reply filed 6/16/2010. UniProt Accession No. Q9H4I2 does not teach a ZHX1 protein.

Response to Arguments - 35 USC § 103

The rejection of claims 1 and 13 under 35 U.S.C. 103(a) as being unpatentable over Tang et al in view of GenBank Accession No. BAA23691.2 has been withdrawn in view of Applicant's amendment to the claims in the reply filed 6/16/2010. The references do not teach a dimer of ZHX3 and ZHX1.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jennifer Dunston whose telephone number is (571)272-2916. The examiner can normally be reached on M-F, 9 am to 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Jennifer Dunston/
Primary Examiner
Art Unit 1636